

Comparison of clinical efficacy and safety of tirzepatide, liraglutide and semaglutide in patients with obesity or overweight and without T2D: A Bayesian network meta-analysis of randomized controlled trials

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SUPPLEMENTARY MATERIAL

Supplementary Tables

Table S1. Eligibility criteria for the systematic literature review (PICOTs)

Domain	Inclusion	Exclusion
Patient population	Adults ≥ 18 years of age with obesity or overweight and at least one weight-related comorbidity	- Individuals < 18 years of age - Individuals without obesity or overweight - Studies with mixed populations with 'overweight/obesity' and 'non-overweight/non-obesity'
Intervention/ Comparators	- Tirzepatide (5 mg, 10 mg, 15 mg QW) - Liraglutide (3 mg QD) - Semaglutide (2.4 mg QW, 50 mg QD) - Mazindol	Any other intervention
Comparators	- Any intervention listed above - Diet and exercise - Placebo	Any other comparator
Outcomes	- Percent change from baseline in body weight (kg) - Absolute change from baseline in body weight (kg) - Percent change from baseline in BMI	Any other outcomes

Domain	Inclusion	Exclusion
	• Absolute change from baseline in BMI • Percentage of participants who achieve $\geq 5\%$ body weight reduction • Percentage of participants who achieve $\geq 10\%$ body weight reduction • Percentage of participants who achieve $\geq 15\%$ body weight reduction • Percentage of participants who achieve $\geq 20\%$ body weight reduction • Mean change from baseline in waist circumference (cm) • Mean change from baseline in Short Form -36 version 2 Health Survey (SF-36v2) acute form Physical Functioning domain score • Mean change from baseline in systolic blood pressure (SBP) (mmHg) • Mean change from baseline in diastolic blood pressure (DBP) (mmHg) • Change from baseline in triglycerides • Change from baseline in HDL • Change from baseline in LDL	• Outcomes not reported separately for the population of interest

Domain	Inclusion	Exclusion
	• Change from baseline in total cholesterol • Change from baseline in HbA1C • Change from baseline in FPG • Percentage of participants who achieve pre-diabetes reversal • Percentage of participants who progress to T2DM • Severe or serious GI AEs • Total GI AEs, including specific AEs such as nausea • Discontinuations due to any reason, lack of efficacy or AEs	
Study duration	≥12 weeks	<12 weeks
Study design	• Randomised controlled trials (RCTs)	• Interventional, non-randomised evidence • Observational and RWE studies
Publication type	• Peer-reviewed primary research <i>Relevant SLRs/NMAs to be included during the title/abstract review for bibliographic hand searching, and then ultimately excluded during the full text review such that the SLR is not ultimately included in the SLR</i>	• Any other publication types, including book chapters, comments, letters, narrative reviews, notes, editorials, case reports, case series

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Domain	Inclusion	Exclusion
Other	- Abstract or full-text published in English - Conference abstracts published in or since 2021	Conference abstracts published prior to 2021

Footnotes: ^a Defined as: hypertension, dyslipidaemia, OSA, ASCVD, prediabetes, hip or knee osteoarthritis, asthma, liver disease (NASH or NAFLD), cerebrovascular disease, disorder of reproductive system, kidney disease, or gout (including hyperuricaemia); ^b Defined as: total cholesterol >5 mmol/L; or HDL <40 mg/dL for men; or <50 mg/dL for women; or SBP >140 mmHg.

Abbreviations: AE, adverse events; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GI, gastrointestinal; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; NMA, network meta-analysis; RCT, randomised controlled trial; RWE, real world evidence; SBP, systolic blood pressure; SLR, systematic literature review; T2DM, type 2 diabetes; QD, once daily; QW, once weekly.

Table S2. Risk-of-bias assessment for studies included in the network meta-analysis based on the Cochrane risk-of-bias tool for randomised trials (RoB-2)^a

Study	Randomisation	Treatment allocation concealment	Similar prognostic factors between groups	Blinding of participants, care providers and outcome assessors	Unexpected imbalances in drop-outs	Reporting of outcome data	Intention-to-treat analysis
O'Neil 2018	Participants were randomly assigned in a 6:1 ratio, through the use of an interactive Web-based response system	An interactive web response system was used	Demographics and baseline characteristics were similar between treatment groups	The study was double-blinded	Discontinuations were reported in the study	All outcomes planned in methods were reported in the study	Efficacy end points were analysed in the full analysis population and safety end points were analysed in the safety analysis population (all randomly assigned participants exposed to at least one dose of liraglutide or placebo)
SCALE Obesity and Prediabetes	Participants were randomly assigned in a 2:1 ratio, use of a telephone or Web-based system provided by the sponsor	A telephone or Web-based system provided by the sponsor was used	Demographics and baseline characteristics were similar between treatment groups	The study was double-blinded	Discontinuations were reported in the study	All outcomes planned in methods were reported in the study	Full analysis set (all randomised participants) has been used for efficacy data analysis. The safety analysis (all randomised participants) exposed to at least 1 doses of the randomised treatment
STEP 1	Participants were randomly assigned in a 2:1 ratio, through the use of an interactive Web-based response system	An interactive web response system was used	Demographics and baseline characteristics were similar between treatment groups	The study was double-blinded	Discontinuations were reported in the study	All outcomes planned in methods were reported in the study	Efficacy end points were analysed in the full analysis population and safety end points were analysed in the safety analysis population (all randomly assigned participants exposed to at least one dose of semaglutide or placebo)
STEP 5	Participants were randomly assigned in a 2:1 ratio, through the use of an interactive web-based response system	An interactive web response system was used	Demographics and baseline characteristics were similar between treatment groups	The study was double-blinded	Discontinuations were reported in the study	All outcomes planned in methods were reported in the study	Efficacy end points were analysed in the full analysis population and safety end points were analysed in the safety analysis population. Multiple Imputation and mixed model for repeated measures were used to account for missing data
STEP 8	Participants were randomised (3:1:3:1) using a blocking schema (block size of 8) via an interactive web response system	An interactive web response system was used	Demographics and baseline characteristics were similar between active treatment groups	The study was double-blinded for semaglutide but liraglutide was open label	Treatment discontinuations have been reported for the study	All outcomes discussed in the methodology have been reported	Efficacy end points were analysed in the full analysis set population and safety end points were analysed in the safety analysis population (all randomly assigned participants exposed to at least one dose of semaglutide or liraglutide or placebo)

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Study	Randomisation	Treatment allocation concealment	Similar prognostic factors between groups	Blinding of participants, care providers and outcome assessors	Unexpected imbalances in drop-outs	Reporting of outcome data	Intention-to-treat analysis
SURMOUNT-1	Participants were randomly assigned in a 1:1:1:1 ratio, through the use of an interactive Web-based response system	An interactive web-based response system was used	Demographics and baseline characteristics were similar between treatment groups	The study was double-blinded	Discontinuations were reported in the study	All outcomes planned in methods were reported in the study	Efficacy end points were analysed in the full analysis population and safety end points were analysed in the safety analysis population (all randomly assigned participants exposed to at least one dose of Tirzepatide 5,10 and 15mg or placebo)

Footnotes: ^a Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *bmj*. 2019;366.

Table S3. Placebo arm results of included studies, efficacy estimand and safety population

Outcome	Population	O'Neil, 2018	SCALE Obesity and Prediabetes	STEP 1	STEP 5	STEP 8	SURMOUNT-1
		Mean CfB	Mean CfB	Mean CfB	Mean CfB	Mean CfB	Mean CfB
Weight (%)	Efficacy estimand	-2.30	-	-2.44	-2.30	-1.80	-2.40
Weight (kg)		-	-	-2.70	-	-1.40	-2.40
BMI (kg/m ²)		-	-	-0.95	-	-	-0.90
Waist circumference (cm)		-	-	-4.48	-	-1.70	-3.40
HbA1c (%)		-	-	-0.16	-	0.10	-0.07
FPG (mg/dL)		-	-	-1.00	-	2.90	0.90
Triglycerides (%)		-	-	-8.00	-	-1.70	-6.30
LDL (%)		-	-	1.00	-	0.80	-0.90
HDL (%)		-	-	2.00	-	-0.50	0.20
Total cholesterol (%)		-	-	0.00	-	-0.20	-1.10
SBP (mmHg)		-	-	-1.14	-	4.50	-1.30
DBP (mmHg)		-	-	-0.59	-	0.30	-1.00
		%	%	%	%	%	%
Weight loss ≥5%	Efficacy estimand	23.00	-	33.07	-	30.43	27.84
Weight loss ≥10%		10.00	-	11.82	-	15.94	13.53
Weight loss ≥15%		4.00	-	5.01	-	5.80	6.07
Weight loss ≥20%		2.00	-	2.00	-	2.90	1.24
Total GI AEs	Safety population	38.00	-	47.90	-	55.30	30.30
Severe GI AEs		-	-	-	-	3.50	1.10
Nausea		18.00	14.70	17.40	-	22.40	9.50
All-cause discontinuation		24.26	35.67	22.44	-	17.60	26.40
Discontinuation due to AE		3.00	3.62	3.10	-	3.50	2.60

Footnotes: “-“ indicates missing data.

Abbreviations: AE, adverse event; BMI, body mass index; CfB, change from baseline; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GI, gastrointestinal; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; LDL, low-density lipoprotein; mmHg, millimetres of mercury; SBP, systolic blood pressure.

Table S4. Placebo arm results of included studies, treatment regimen estimand

Outcome	O'Neil, 2018		SCALE Obesity and Prediabetes		STEP 1		STEP 5		STEP 8		SURMOUNT-1	
	Mean CfB	SE	Mean CfB	SE	Mean CfB	SE	Mean CfB	SE	Mean CfB	SE	Mean CfB	SE
Weight (%)	-2.30	0.74	-2.60	0.16	-2.41	–	-3.30	0.56	-1.90	1.07	-3.10	0.61
Weight (kg)	-2.48	0.82	-2.80	0.19	-2.60	–	-3.50	0.65	-1.60	1.20	-2.99	0.64
BMI (kg/m ²)	-0.88	0.29	-1.00	0.07	-0.92	–	-1.30	0.23	–	–	-1.15	0.24
Waist circumference (cm)	-3.47	0.81	-3.90	0.19	-4.13	–	-4.50	0.60	-2.00	1.05	-4.00	0.59
HbA1c (%)	-0.01	0.03	-0.06	0.01	-0.15	–	-0.22	0.04	0.10	0.03	-0.09	0.02
FPG (mg/dL)	0.18	0.90	0.10	0.30	-0.48	–	–	–	3.30	1.38	0.41	0.67
Triglycerides (%)	-5.00	3.00	-5.50	–	-7.00	–	–	–	-3.20	4.39	-5.60	2.23
LDL (%)	-3.00	2.00	-1.00	–	1.00	–	–	–	-1.10	5.56	-1.67	1.51
HDL (%)	0.00	1.00	0.70	–	1.00	–	–	–	-0.90	1.89	-0.68	1.12
Total cholesterol (%)	-3.00	1.00	-1.00	–	0.00	–	–	–	-3.30	2.40	-1.78	0.97
SBP (mmHg)	-1.58	1.04	-1.50	0.35	-1.06	–	-0.72	2.54	3.20	1.48	-1.00	0.68
DBP (mmHg)	-1.50	0.73	-1.90	0.25	-0.42	–	-0.86	1.73	0.70	1.12	-0.82	0.42
	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N
Weight loss ≥5%	31 (23.00)	136	332 (27.10)	1225	182 (31.50)	577	38 (29.50)	129	23 (29.50)	78	222 (34.50)	643
Weight loss ≥10%	14 (10.00)	136	130 (10.60)	1225	69 (12.00)	577	17 (13.20)	129	12 (15.40)	78	121 (18.80)	643
Weight loss ≥15%	7 (5.00)	136	43 (3.50)	1225	28 (4.90)	577	7 (5.40)	129	5 (6.40)	78	57 (8.80)	643
Weight loss ≥20%	3 (2.00)	136	–	–	10 (1.70)	577	3 (2.30)	129	2 (2.60)	78	20 (3.10)	643
Prediabetes reversal	–	–	244 (33.00)	738	126 (47.80)	263	–	–	–	–	167 (61.85)	270

Footnotes: “–” indicates missing data.

Abbreviations: BMI, body mass index; CfB, change from baseline; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; mmHg, millimetres of mercury; n; total number of events; N, total number of individuals; SBP, systolic blood pressure; SE, standard error.

Table S5. Studies reporting on efficacy outcomes, efficacy estimand

Trial	CfB in weight (kg)	CfB in weight (%)	CfB in BMI (kg/m ²)	≥5% weight reduction	≥10% weight reduction	≥15% weight reduction	≥20% weight reduction	CfB in waist circumference (cm)	CfB in HbA1c (%)	CfB in FPG (mg/dL)	Prediabetes with reversal	CfB in triglycerides (%)	CfB in LDL (%)	CfB in HDL (%)	CfB in total cholesterol (%)	CfB in SBP (mmHg)	CfB in DBP (mmHg)
O'Neil, 2018	N	Y	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N
SCALE Obesity and Prediabetes	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
STEP 1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
STEP 5	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
STEP 8	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
SURMOUNT-1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Total	3	5	2	4	4	4	4	3	3	3	1	3	3	3	3	3	3

Abbreviations: CfB, change from baseline; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure.

Table S6. Studies reporting on safety outcomes

Trial	Total GI AEs	Severe GI AEs	Nausea AEs	All-cause discontinuation	Discontinuation due to AEs
O'Neil, 2018	Y	N	Y	Y	Y
SCALE Obesity and Prediabetes	N	N	Y	Y	Y
STEP 1	Y	N	Y	Y	Y
STEP 5	N	N	N	N	N
STEP 8	Y	Y	Y	Y	Y
SURMOUNT-1	Y	Y	Y	Y	Y
Total	4	2	5	5	5

Footnotes: All AEs refer to the number of participants reporting events, not the number of events.

Abbreviations: AE, adverse event; GI, gastrointestinal.

Table S7. Studies reporting on efficacy outcomes, treatment regimen estimand

Trial	CfB in weight (kg)	CfB in weight (%)	CfB in BMI (kg/m ²)	≥5% weight reduction	≥10% weight reduction	≥15% weight reduction	≥20% weight reduction	CfB in waist circumference (cm)	CfB in HbA1c (%)	CfB in FPG (mg/dL)	Prediabetes with reversal	CfB in triglycerides (%)	CfB in LDL (%)	CfB in HDL (%)	CfB in total cholesterol (%)	CfB in SBP (mmHg)	CfB in DBP (mmHg)
O'Neil, 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
SCALE Obesity and Prediabetes	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
STEP 1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
STEP 5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	Y
STEP 8	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
SURMOUNT-1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Total	6	6	5	6	6	6	5	6	6	6	3	5	5	5	5	5	6

Abbreviations: BMI, body mass index; CfB, change from baseline; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure.

Table S8. NMA results: Treatment regimen estimand, random effects models

Category	Outcome [Outcome Measure]	Tirzepatide versus Comparators					
		Tirzepatide 5 mg QW		Tirzepatide 10 mg QW		Tirzepatide 15 mg QW	
		Liraglutide 3 mg QD	Semaglutide 2.4 mg QW	Liraglutide 3 mg QD	Semaglutide 2.4 mg QW	Liraglutide 3 mg QD	Semaglutide 2.4 mg QW
Weight reduction	CfB in weight (kg) [MD]	-6.48 (-9.06, -2.69)	0.95 (-1.59, 4.90)	-11.19 (-13.74, -7.26)	-3.75 (-6.27, 0.34)	-12.86 (-15.41, -8.89)	-5.43 (-7.92, -1.26)
	CfB in weight (%) [MD]	-6.33 (-9.14, -2.38)	1.27 (-1.33, 5.57)	-10.78 (-13.59, -6.66)	-3.19 (-5.79, 1.27)	-12.19 (-14.96, -8.05)	-4.59 (-7.16, -0.11)
	CfB in BMI (kg/m ²) [MD]	-2.46 (-4.44, 0.26)	0.18 (-1.84, 2.84)	-4.15 (-6.10, -1.42)	-1.51 (-3.51, 1.17)	-4.77 (-6.71, -1.99)	-2.13 (-4.13, 0.56)
	≥5% weight reduction [OR]	2.38 (1.20, 4.66)	0.69 (0.33, 1.30)	3.32 (1.67, 6.60)	0.96 (0.45, 1.84)	4.20 (2.08, 8.42)	1.21 (0.57, 2.35)
	≥10% weight reduction [OR]	2.59 (1.30, 5.75)	0.55 (0.26, 1.16)	4.24 (2.10, 9.40)	0.90 (0.43, 1.91)	6.00 (2.98, 13.40)	1.27 (0.60, 2.70)
	≥15% weight reduction [OR]	2.58 (1.19, 6.41)	0.42 (0.18, 0.97)	5.61 (2.58, 13.95)	0.91 (0.39, 2.12)	6.74 (3.10, 16.78)	1.10 (0.47, 2.56)
	≥20% weight reduction [OR]	5.99 (1.73, 21.65)	0.53 (0.19, 1.44)	14.11 (4.07, 50.81)	1.26 (0.45, 3.37)	18.31 (5.29, 65.75)	1.63 (0.58, 4.37)
Cardiometabolic	CfB in waist circumference (cm) [MD]	-5.45 (-7.97, -1.85)	0.04 (-2.41, 3.77)	-9.10 (-11.61, -5.40)	-3.62 (-6.07, 0.21)	-9.92 (-12.38, -6.25)	-4.43 (-6.84, -0.60)
Glycaemic parameters	CfB in HbA1c (%) [MD]	-0.04 (-0.15, 0.05)	0.04 (-0.07, 0.14)	-0.12 (-0.23, -0.03)	-0.05 (-0.15, 0.06)	-0.12 (-0.23, -0.03)	-0.05 (-0.15, 0.06)
	CfB in FPG (mg/dL) [MD]	0.33 (-5.07, 7.88)	2.37 (-2.93, 10.60)	-1.93 (-7.18, 5.87)	0.12 (-5.06, 8.64)	-2.19 (-7.46, 5.69)	-0.15 (-5.32, 8.32)
	Prediabetes with reversal [OR]	2.01 (0.39, 10.13)	1.57 (0.29, 8.03)	1.68 (0.32, 8.29)	1.31 (0.25, 6.64)	2.05 (0.40, 10.24)	1.60 (0.30, 8.20)

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Category	Outcome [Outcome Measure]	Tirzepatide versus Comparators					
		Tirzepatide 5 mg QW		Tirzepatide 10 mg QW		Tirzepatide 15 mg QW	
		Liraglutide 3 mg QD	Semaglutide 2.4 mg QW	Liraglutide 3 mg QD	Semaglutide 2.4 mg QW	Liraglutide 3 mg QD	Semaglutide 2.4 mg QW
Lipids	CfB in triglycerides (%) [MD]	-5.00 (-12.45, 4.12)	3.03 (-4.78, 12.66)	-7.57 (-14.92, 1.72)	0.51 (-7.29, 10.25)	-12.73 (-19.92, -3.26)	-4.67 (-12.23, 5.25)
	CfB in LDL (%) [MD]	-1.02 (-8.47, 6.49)	2.18 (-5.27, 10.91)	-2.07 (-9.44, 5.58)	1.13 (-6.24, 9.89)	-3.47 (-10.74, 4.29)	-0.26 (-7.57, 8.62)
	CfB in HDL (%) [MD]	5.05 (-4.37, 11.02)	4.18 (-4.93, 11.20)	7.16 (-2.52, 13.16)	6.32 (-3.05, 13.27)	6.07 (-3.39, 11.93)	5.20 (-3.94, 12.10)
	CfB in total cholesterol (%) [MD]	-1.01 (-8.57, 6.16)	2.02 (-5.21, 10.35)	-1.56 (-9.07, 5.62)	1.47 (-5.75, 9.87)	-3.32 (-10.70, 4.02)	-0.31 (-7.36, 8.24)
Blood pressure	CfB in SBP (mmHg) [MD]	-2.11 (-6.12, 4.23)	0.43 (-3.76, 6.78)	-3.21 (-7.29, 3.18)	-0.68 (-4.85, 5.78)	-2.95 (-6.96, 3.42)	-0.43 (-4.58, 6.00)
	CfB in DBP (mmHg) [MD]	-3.34 (-7.12, 1.12)	-0.81 (-4.26, 4.17)	-3.42 (-7.16, 1.08)	-0.88 (-4.34, 4.13)	-2.97 (-6.73, 1.53)	-0.43 (-3.89, 4.59)

Footnotes: **Dark green** indicates where tirzepatide performed statistically better compared to the comparator; **light green** indicates where tirzepatide performed numerically better compared to the comparator; **dark red** indicates where tirzepatide performed statistically worse compared to the comparator; **light red** indicates where tirzepatide performed numerically worse compared to the comparator.

Abbreviations: BMI, body mass index; CfB, change from baseline; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MD, mean difference; mmHg, millimetres of mercury; SBP, systolic blood pressure.

Table S9. Arm-level results for active treatments of included studies, efficacy estimand

Outcome	O'Neil, 2018	SCALE Obesity and Prediabetes	STEP 1	STEP 5	STEP 8		SURMOUNT-1		
	Mean CfB	Mean CfB	Mean CfB	Mean CfB					
	Liraglutide 3.0 mg	Liraglutide 3.0 mg	Semaglutide 2.4 mg	Semaglutide 2.4 mg	Liraglutide 3.0 mg	Semaglutide 2.4 mg	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
Weight (%)	-9.20	-9.20	-16.86	-16.60	-6.6	-17.1	-16.0	-21.4	-22.5
Weight (kg)	-	-	-17.40	-	-6.7	-16.7	-16.1	-22.2	-23.6
BMI (kg/m ²)	-	-	-6.27	-	-	-	-5.9	-8.1	-8.6
Waist circumference (cm)	-	-	-15.22	-	-6.8	-14.7	-14.6	-19.4	-19.9
Prediabetes reversal ^a	-	69.0%	84.1%	-	64.9%	89.5%	93.5%	92.4%	93.7%
HbA1c (%)	-	-	-0.50	-	-0.1	-0.3	-0.4	-0.49	-0.51
FPG (mg/dL)	-	-	-9.90	-	-6.5	-9.8	-7.7	-9.7	-10.6
Triglycerides (%)	-	-	-24.00	-	-12.5	-20.8	-24.3	-27.0	-31.4
LDL (%)	-	-	-4.00	-	0.6	-7.8	-5.3	-6.6	-8.6
HDL (%)	-	-	5.00	-	1.6	-1.2	7.0	8.6	8.2
Total cholesterol (%)	-	-	-4.00	-	-0.5	-8.2	-4.9	-5.6	-7.4
SBP (mmHg)	-	-	-7.08	-	-5.4	-6.6	-7.4	-8.8	-8.0
DBP (mmHg)	-	-	-2.99	-	-1.3	-4.2	-5.3	-5.8	-4.7

Footnotes: ^a Prediabetes reversal was assessed only in the patients who had prediabetes at baseline, with N given in each case, and treatment regimen estimand results are presented, given efficacy estimand results were not available for all studies other than SURMOUNT-1.

Abbreviations: BMI, body mass index; CfB, change from baseline; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; LDL, low-density lipoprotein; mmHg, millimetres of mercury; n, total number of events; N, total number of individuals; SBP, systolic blood pressure; SE, standard error.

Table S10. NMA NNT results: Efficacy estimand and safety outcomes, random effect models

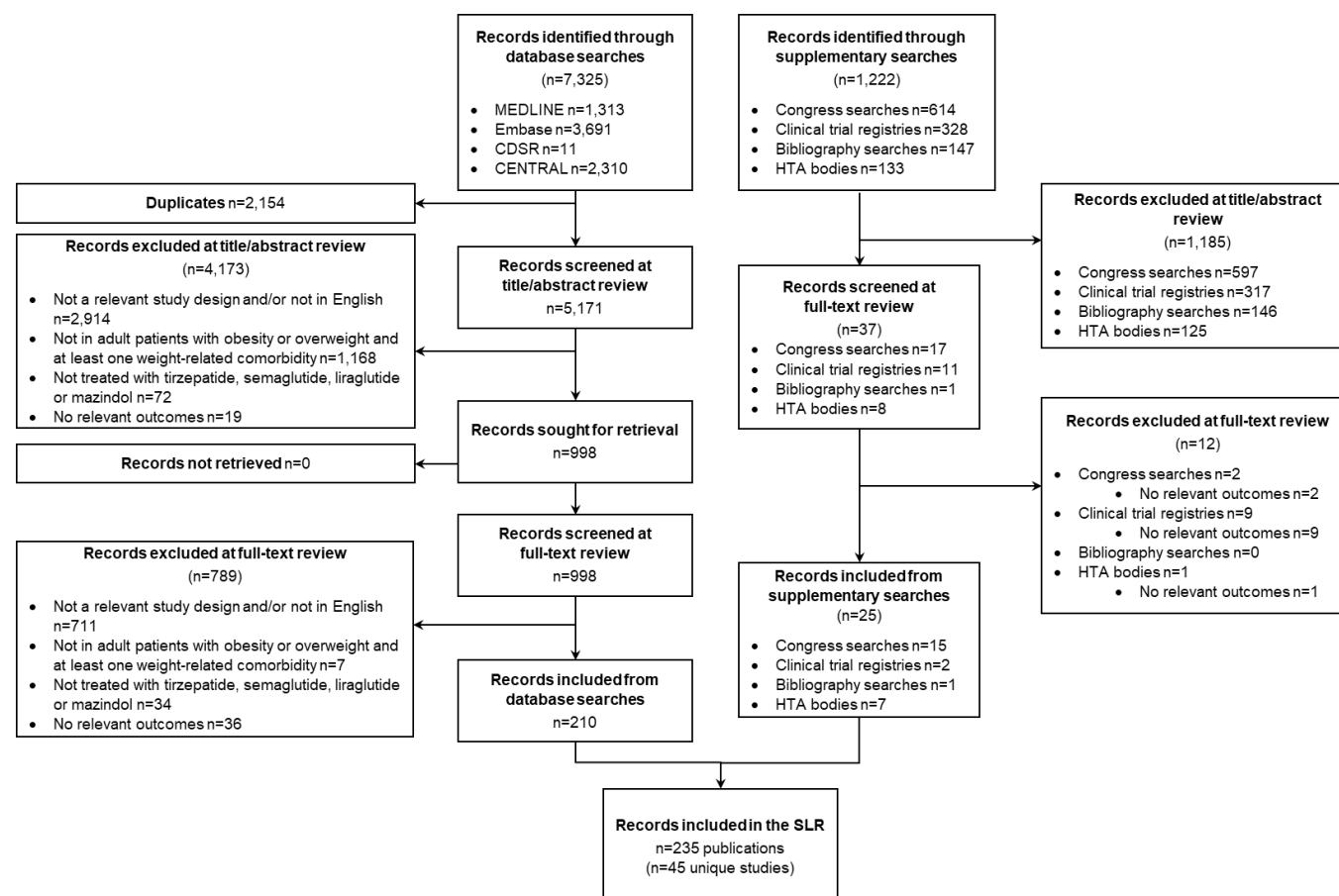
Outcome	Number needed to treat versus placebo				
	Tirzepatide 5 mg QW	Tirzepatide 10 mg QW	Tirzepatide 15 mg QW	Liraglutide 3 mg QD	Semaglutide 2.4 mg QW
≥5% weight reduction ^a	1.63 (1.48, 1.99)	1.47 (1.39, 1.59)	1.46 (1.39, 1.59)	2.42 (1.88, 3.93)	1.59 (1.48, 1.78)
≥10% weight reduction ^a	1.67 (1.37, 2.55)	1.38 (1.25, 1.74)	1.31 (1.22, 1.54)	4.14 (2.36, 11.01)	1.56 (1.37, 2.01)
≥15% weight reduction ^a	2.27 (1.56, 4.24)	1.48 (1.24, 2.11)	1.39 (1.20, 1.87)	6.75 (3.03, 21.12)	1.78 (1.40, 2.55)
≥20% weight reduction ^a	3.21 (1.61, 9.23)	1.81 (1.24, 3.95)	1.60 (1.18, 3.16)	49.51 (-171.90, 530.20)	4.19 (2.03, 11.08)

Footnotes: ^aModel used an informative prior for between-study standard deviation.

Abbreviations: NNT, number needed to treat; QD, once daily; QW, once weekly.

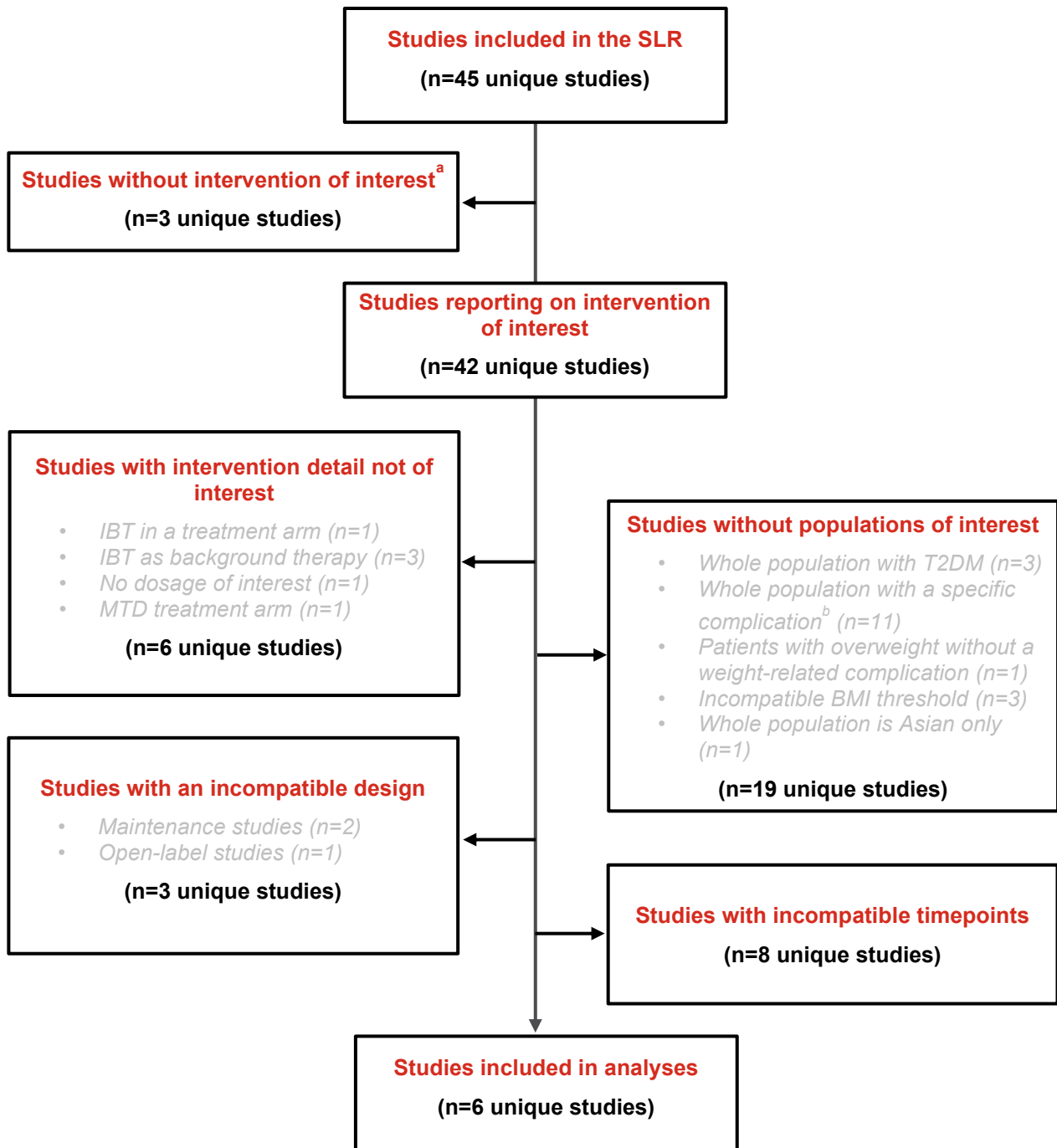
Supplementary Figures

Figure S1. SLR PRISMA diagram



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Figure S2. Flowchart for study inclusion as assessed during the feasibility assessment

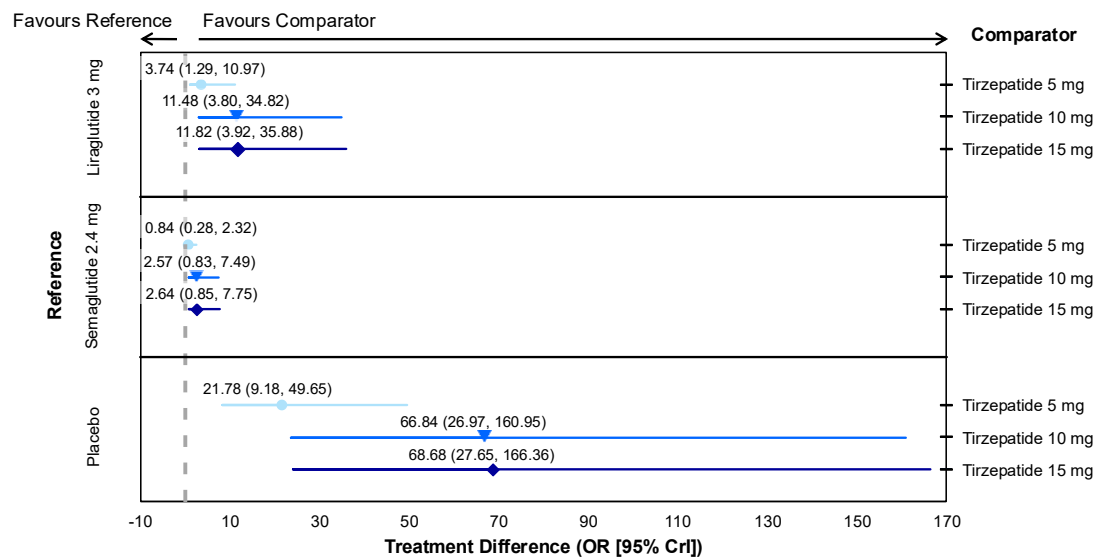


Footnotes: ^aThe SLR inclusion criteria were slightly broader and included three studies that included mazindol as the only active intervention. ^bThe specific complications were binge eating disorder, COPD, gastrectomy, gastric bypass, heart failure, knee osteoarthritis, NAFLD, psychosis and schizophrenia.

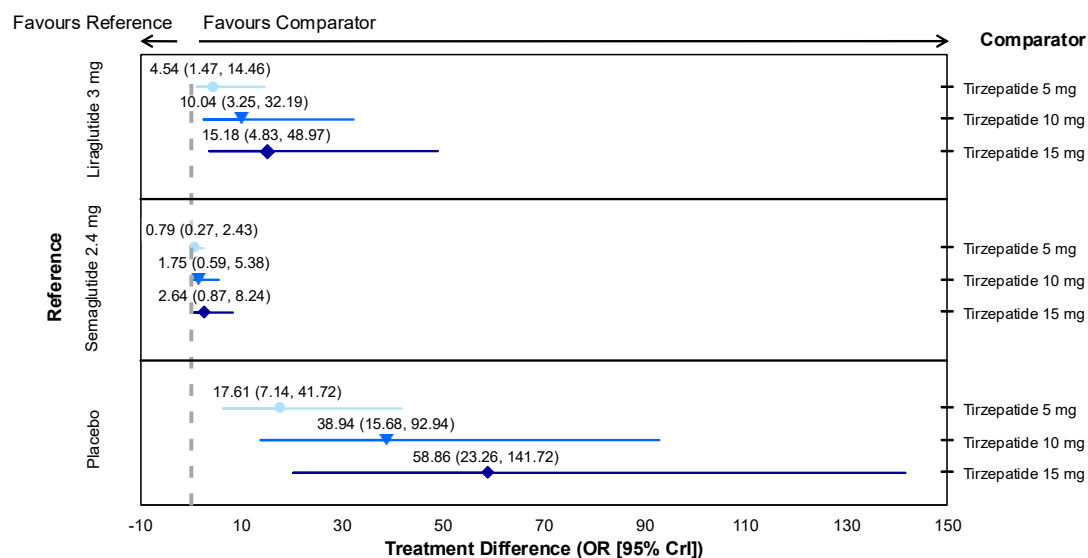
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disorder; IBT, intensive behavioural therapy; MTD, maximum tolerated dose; NAFLD, non-alcoholic fatty liver disease; SLR, systematic literature review; T2DM, type 2 diabetes mellitus.

Figure S3. Additional forest plots (efficacy estimand) OR and 95% CrI for RE unadjusted models

(a) $\geq 5\%$ weight reduction

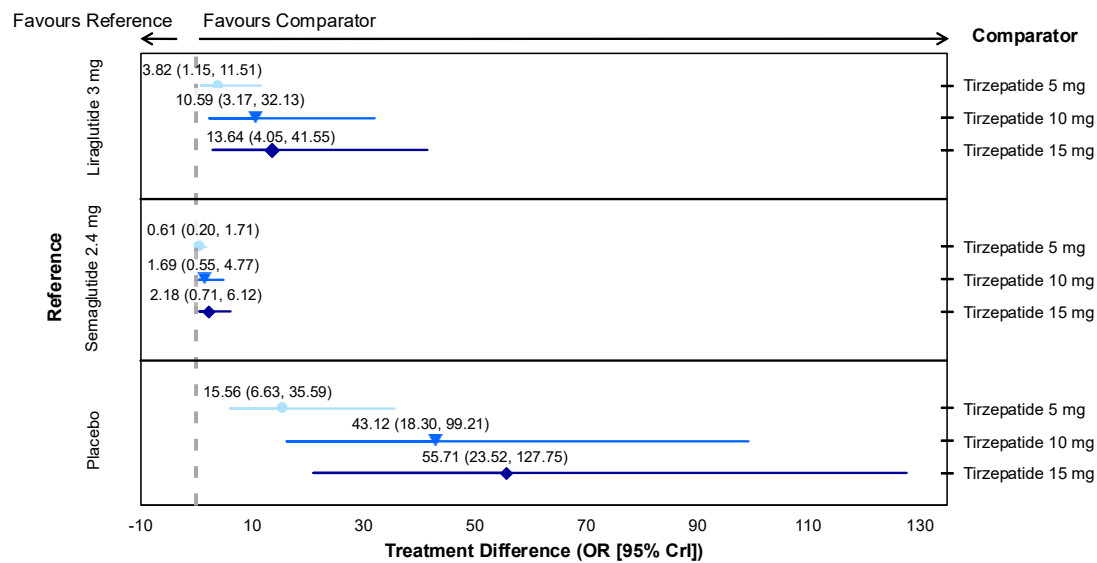


(b) $\geq 10\%$ weight reduction

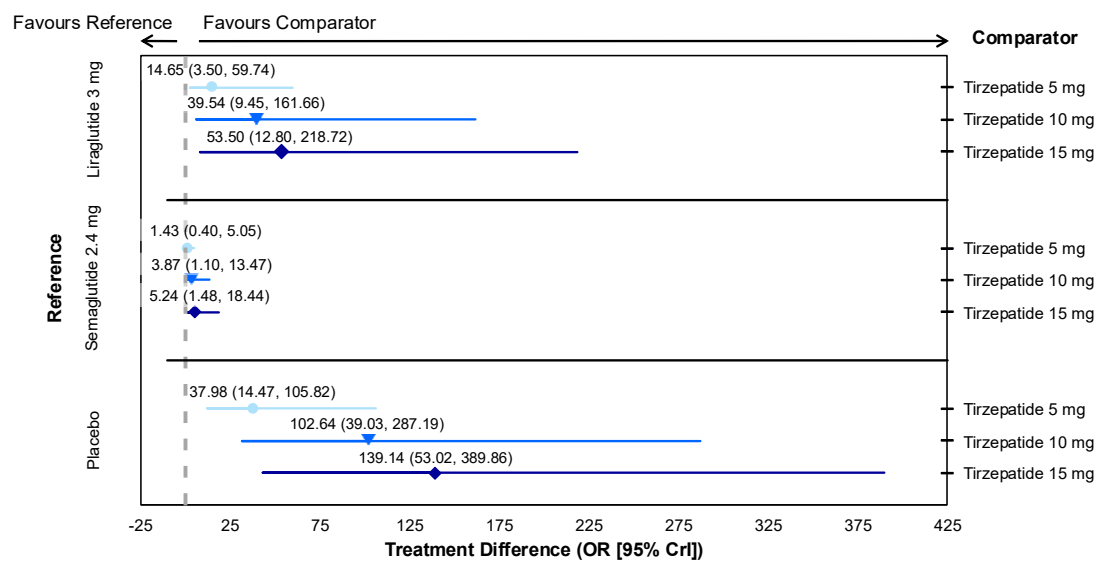


Comparison of clinical efficacy and safety of tirzepatide, liraglutide and semaglutide in patients with obesity – Supplementary Material

(c) $\geq 15\%$ weight reduction



(d) $\geq 20\%$ weight reduction



Abbreviations: CrI, credible interval; OR, odds ratio; RE, random effects.

Supplementary Materials

Material S1: Simulation Parameters and Convergence Diagnostics

For each analysis, three chains with different sets of initial values were used and an initial 20,000 iterations were run as a burn-in period to achieve convergence. The burn-in was then discarded and the analysis results based on a further 60,000 iterations per chain with a thinning factor of 1 for a total of 180,000 iterations. Further iterations were conducted if required.

Convergence was assessed using history trace plots, smoothed Kernel posterior plots and Brook-Gelman-Rubin (BGR) diagnostic plots.¹⁻³

History trace plots of the parameters of interest display the evolution of the variables against iteration number and are a good tool to assess for non-convergence in the simulation. The plots must show all the characteristics of a random series: no trend over iteration number, values well-dispersed in space and which do not remain localised as iteration number increases.

The smoothed Kernel density plots were inspected and must show that the posterior density functions of each parameter of interest are approximately globally unimodal and symmetric. This will confirm whether convergence towards a sensible posterior distribution has been achieved. In particular, convergence of the posterior distributions of the between-study SDs were checked for all RE models.

Auto-correlation plots were used to assess the dependence between successive iterations of the Markov chains and Monte Carlo standard errors were checked to ensure sufficient information had been sampled. In particular, it was ensured that Monte Carlo SEs were less than 5% of the standard deviations of the basic model parameters.⁴

The BGR diagnostic plots were used to assess the within-chain and between-chain variability. Once the chains have converged, this variability should be approximately equal to one and should be stable across iterations.

References

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2. Brooks, S; Gelman, A. General Methods for Monitoring Convergence of Iterative Simulations. J Comput Graphi Stat. 1998;7:434-455.
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